REMARKS/ARGUMENTS

The Office Action dated February 26, 2003 has been carefully reviewed. Claims 2, 4-16 and 20-22 are presented for prosecution. No claims stand allowed. This rejection has been made final.

Claims 2, 4-16 and 20-22 are rejected under 35 U.S.C. §103(a) as being unpatentable over Badwan *et al.* (5,646,131). The Examiner has pointed out that Badwan *et al.* discloses poorly water soluble active agent compositions comprising a cyclodextrin, a water soluble acid and a water soluble organic polymer and concludes that the amounts of these ingredients are within the ranges claimed in applicant's claims, except for the water soluble acid. The Examiner then attempts to equate applicant's claimed compositions with those disclosed in Badwan *et al.* by stating that Badwan *et al.* teaches that the acid must be in sufficient quantity to form aggregates in order for enhancement of solubility to occur.

Applicant's claimed invention relates to a pharmaceutical composition comprising a sparingly water-soluble drug compound, a cyclodextrin, an acid and a water-soluble organic polymer. The acid in the composition on exposure to water generates a low pH environment in which the solubility of the drug is increased. The acidic microenvironment contains cyclodextrin which is capable of complexing the solubilized drug causing the production of a supersaturated solution of the drug compound. The supersaturated solution is stabilized by the viscosity enhancing effects of the organic polymer which hinders precipitation of the drug as the pH increases, as the microenvironment becomes more dilute as more water enters. As a result, the drug compound is made readily bioavailable to the organism to which it is to be administered.

The Examiner has stated that the '131 patent "teaches poorly water soluble active agent compositions comprising a cyclodextrin, a water soluble acid, and a water soluble organic polymer wherein, except for the water soluble acid, the amounts of these ingredients are within the instant ranges". The Examiner cites as support for this conclusion the Abstract; col. 3, lines 58-63; col. 4, lines 6-21 and 62-67; col. 5, lines 5-9 and 24-44; col. 6, lines 18-29; and Example 4. The Examiner has correctly pointed out, however, that the amount of water soluble acid in the Badwan *et al.* formulation is not within the ranges of the acid in applicant's formulation.

In column 5, lines 50 to 62 of Badwan *et al.* it is disclosed that the typical compositions comprise acid at a concentration of about 0.1 to about 5% total weight. Only in selected solid dosage forms are considerably greater amounts of acid employed, i.e. from 5 to about 10% by weight, as a solubilization enhancer. Greater amounts of the acid can be present in the Badwan *et al.* compositions, but only if that ingredient is serving another purpose in the composition other than as a solubilizing agent. For example greater amounts of the acid are used in Badwan *et al.* as an effervescing agent (col. 5, lines 60-63). Since in Badwan *et al.* the acid is present in concentrations of at most 10% by weight for the purpose of solubilizing the drug, one skilled in the art would not be motivated to increase the amount of acid in order to increase solubility because Badwan *et al.* clearly states that amounts of acid greater than 10% are used for other

purposes. In applicant's compositions the acid is present in an amount from 35% to 95%, which is considerably higher than the maximum amount employed in Badwan *et al.* It is submitted that Badwan *et al.* actually teaches away from exploring the use of greater amounts than 10% of acid in order to increase solubility.

It should also be noted that the water soluble organic polymer is not an integral part of the composition disclosed in Badwan *et al.* No mention of a water soluble polymer is made in any of the claims in Badwan *et al.* In addition, only examples 2 and 4 in Badwan *et al.* contain a water soluble polymer. In the preparation of syrups in Example 2 it is stated that "syrups typically contain sufficient viscosity imparting agents (such as polyvinylpyrrolidone) in an amount of from about 1 to about 3% of the syrup." The water soluble polymer in the Badwan *et al.* compositions, therefore, is merely an additive.

In rejecting the claims the Examiner makes reference to EP 0 689,844. (See page 3, paragraph 5, line 2 of he office action.) The '844 patent relates to pharmaceutical compositions containing an inclusion complex of vinpocetine formed with a cyclodextrin. The inclusion complex is preferably dispersed in a polymer matrix that provides modified, *i.e.* extended, release of the active agent or is dispersed onto inert microspheres and coated with a rate controlling polymer. Although the compositions of the reference may contain a limited amount of acid, the acid is used to prepare the vinpocetine-cyclodextrin complexes. The acid is not an integral part of the '844 composition since the acid used to prepare the vinpocetine-cyclodextrin complex may be neutralized with NaOH prior to isolating the finished complex (see Example 2). Applicant's claimed compositions contain an amount of water soluble acid far in excess of any residual acid that may remain in the vinpocetine complexes.

The Examiner then concludes that it would have been obvious to one skilled in the art to adjust the amount of water soluble acid in the formulation disclosed in the '844 patent in order to provide a "sufficient quantity of acid to form aggregates for enhancement of solubility". Although the compositions of the reference may contain a limited amount of acid, the acid is used to prepare the vinpocetine-cyclodextrin complexes. As indicated above, the acid is not an integral part of the '844 compositions since the acid used to prepare the vinpocetine-cyclodextrin complex may be neutralized with NaOH prior to isolating the finished complex. Since there is little or no acid in the resultant complex, one skilled in the art would not have been motivated to adjust the amount of water soluble acid in the formulation described in the '844 patent in order to provide a sufficient quantity of acid to form aggregates for the enhancement of solubility. As pointed out above, in Example 2 of the '844 patent the acid is actually neutralized with NaOH prior to isolating the complex.

Since in the preparation of the complex in the '844 patent the solution may be neutralized prior to being dispersed in a polymer matrix or being dispersed onto inert microspheres coated with a rate-controlling polymer (see Example 2), there is no incentive to increase the amount of acid in the formulation to achieve greater solubility as suggested by the Examiner. Thus on exposure to water there is no acid present in the composition prepared in Example 2 to assist complexation of the solubilized drug.

Although Badwan *et al.* does not teach that the release profile would be different from that of applicant's composition, it is clear that in the Badwan *et al.* formulations containing amounts of acid greater than 10%, the acid is not present for the purpose of enhancing the solubility of the drug but for some other purpose such as effervescence. Since applicant's formulation is not an effervescent composition, it is submitted that a comparison of the release profiles of the formulations would not be meaningful. In addition, there would be no motivation to adjust the amount of acid in the formulation in the '131 patent to the levels contained in applicant's composition, since Badwan *et al.* actually teaches away from exploring greater amounts of acid in order to increase solubility. As indicated above in column 5, lines 60-63 of the '131 patent it is disclosed that amounts of the acid greater than 10% serve a different purpose. Applicant's composition, therefore, is not obvious over the disclosure in Badwan *et al.*

Reconsideration of the rejection of Claims 2, 4-16 and 20-22 under 35 U.S.C. §103(a) as being unpatentable over Badwan *et al.* is courteously requested.

Claims 2, 4-16 and 20-22 are rejected under 35 U.S.C. §103(a) as being unpatentable over De Sousa Goucha Jorge (EP 0 689 844) in view of Badwan *et al.* (5,646,131). This is essentially the same rejection as that set forth above since the Examiner relies on the same references for obviousness.

The Examiner has stated that the '844 reference "teaches poorly water soluble active agent compositions comprising a cyclodextrin, a water soluble acid, and a water soluble organic polymer wherein, except for the water soluble acid, the amounts of these ingredients are within the instant ranges". The Examiner cites as support for this conclusion the abstract; page 2, lines 25-43; page 3, lines 4-14; example 7; and the claims of the '844 reference. As indicated above, the water soluble acid is not an integral part of the '844 complex since it can be neutralized during formation of the complex.

According to the abstract on page 1 of the reference the invention "relates to pharmaceutical compositions, useful in the treatment of cerebrovascular disorders, containing an inclusion complex of vinpocetine formed with any kind of cyclodextrin". There is no reference to the inclusion of a water-soluble acid in the complex. The reference even fails to include any reference to a water soluble acid in the claims drawn to the process for preparing the inclusion complex, *i.e.* claims 6, 15 and amended claims 5 and 14.

With regard to the release profile, the Examiner has concluded that neither reference provides an indication of a release profile that would differ from the instant release profile and states that motivation to adjust the amounts of ingredients within the instant claimed ranges is provided. Applicant submits that there is no motivation in either Badwan *et al.* or the '844 patent to increase the amount of water soluble acid to the present claimed range in order to enhance the solubility of the drug. Badwan *et al.* uses amounts of water soluble acid exceeding 10% only in the preparation of effervescent tablets. A water soluble acid is not an integral part of the complex disclosed in the '844 patent. Increasing the amount of polymer (methocel) in the '844 patent results in only a

minimal decrease in the dissolution rate of the drug. It is submitted that there is no provision in either Badwan *et al.* or the '844 patent of any motivation to adjust the amounts of ingredients within the instant claimed ranges as suggested by the Examiner.

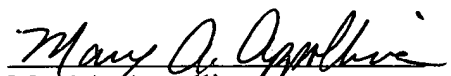
Applicant submits that the '131 patent does not provide any motivation to adjust the water soluble acid in the '844 patent to provide a sufficient quantity of acid to form aggregates for enhancement of solubility (said sufficient quantity, as already indicated above, is taught to be limited to 10 %), as suggested by the Examiner, since the inclusion complex in the '844 patent may contain little or no water soluble acid. The composition disclosed in the '844 patent does not require the water soluble acid to be an integral part of the composition. Badwan *et al.* employs greater amounts of the water soluble acid, i.e. over 10 %, for purposes other than enhancing the solubility of the drug. It is submitted that one skilled in the art at the time of the invention would not have been motivated to adjust the amount of water soluble acid in the complex of the '844 patent to provide a sufficient quantity of acid to form aggregates for the enhancement of solubility. The complex of the '844 patent does not require the presence of a water soluble acid. Applicant's claimed composition, therefore, is not obvious over the '844 patent in view of Badwan *et al.*

Reconsideration of the rejection of Claims 2, 4-16 and 20-22 under 35 U.S.C. §103(a) as being unpatentable over De Sousa Goucha Jorge (EP O 689 844) in view of Badwan *et al.* (5,646,131) is courteously requested.

Claim 21 is being canceled without prejudice by the present amendment.

In view of the above discussion and the amendment herein being made to the claims, it is believed that all of the outstanding objections and rejections have been removed. A favorable disposition of this application is courteously requested. In the event the Examiner adheres to the Final Rejection, entry of the amendment is requested in order to make the record on appeal complete.

Respectfully submitted



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